

Davis, N.
09/819252

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(FILE 'CAPLUS' ENTERED AT 11:02:15 ON 28 JAN 2002)

L1 365 SEA FILE=CAPLUS ABB=ON PLU=ON CDX2 OR CDX 2
L2 36 SEA FILE=CAPLUS ABB=ON PLU=ON L1 AND (CANCER? OR
CARCIN? OR NEOPLAS? OR TUMOUR OR TUMOR)
L3 18 SEA FILE=CAPLUS ABB=ON PLU=ON L2 AND (DETERM? OR
DETECT? OR DET## OR SCREEN? OR DIAGNOS?)

L3 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:59305 CAPLUS
TITLE: The Caudal-related homeodomain protein CDX1
activates proliferating cell nuclear antigen
expression in hepatocellular and colorectal
carcinoma cells
AUTHOR(S): Oh, Eun-Jin; Park, Jae-Hong; Cho, Mong; Lee,
Won-Jae; Choi, Yung Hyun; Yoo, Mi-Ae
CORPORATE SOURCE: Department of Molecular Biology, Pusan National
University, Pusan, 609-735, S. Korea
SOURCE: International Journal of Oncology (2002), 20(1),
23-29
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cdx1 and **Cdx2** are known as Caudal-related homeodomain
transcription factors important in the early differentiation and
maintenance of intestinal epithelial cells. Cdx1 and **Cdx2**
are expressed in the small intestine and colon of fetus and adult.
Most previous studies suggested that **Cdx2** inhibits
proliferation. Several target genes of **Cdx2** have been
identified. However, the effect of Cdx1 on cell proliferation is
currently controversial and its target genes except for Hox-A7
remain unknown. In this study, we found several potential
Caudal-related homeodomain binding sequences in the 5-flanking
region of human PCNA gene. Cotransfection expts., using human PCNA
reporter plasmid and CDX1 and **CDX2** expression plasmids,
showed that CDX1 transactivates human PCNA gene promoter activity in
hepatocellular cell line (HepG2) and colorectal **carcinoma**
cell lines (Colo320HSR and HCT116), while **CDX2** does not.
CDX1-induced PCNA expression was also **detected** in
immunoblot and cytochem. expts. In BrdU incorporation expts., CDX1
enhanced the incorporated BrdU. Taken together, our results suggest
that CDX1 have a pro-proliferative effect on proliferation through
transactivation of PCNA promoter activity.

L3 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:41281 CAPLUS
TITLE: Ectopic expression of homeodomain protein
CDX2 in intestinal metaplasia and
carcinomas of the stomach
AUTHOR(S): Bai, Yun-Qing; Yamamoto, Hiroshi; Akiyama,
Yoshimitsu; Tanaka, Hiroyuki; Takizawa,
Touichirou; Koike, Morio; Kenji Yagi, Osmar;
Saitoh, Kiyoshi; Takeshita, Kimiya; Iwai,
Takehisa; Yuasa, Yasuhito
CORPORATE SOURCE: Graduate School of Medicine and Dentistry,
Department of Surgery, Tokyo Medical and Dental
University, Tokyo, Japan
SOURCE: Cancer Letters (Shannon, Ireland) (2002),

Searcher : Shears 308-4994

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PUBLISHER: 176(1), 47-55
DOCUMENT TYPE: CODEN: CALEDQ; ISSN: 0304-3835
LANGUAGE: Elsevier Science Ireland Ltd.
Journal
English

AB The roles of **CDX2** and **CDX1** homeobox genes during gastric **carcinogenesis** remain poorly defined. We have studied the expression of **CDX2/1** in gastric **cancers** and intestinal metaplasia (IM) of 69 gastric **carcinoma** patients by immunohistochem. **CDX2/1** were shown to be ectopically overexpressed in IM in 41 (85%) of 48, and 47 (90%) of 52 cases, resp. The expression of **CDX2/1** was detected in 38 (55%) and 51 (74%) of the 69 gastric **carcinomas**, resp. The histol. type of the gastric **carcinomas** was independently assocd. with **CDX2** expression, but not with that of **CDX1**, with higher **CDX2** expression in intestinal type (differentiated type) than in diffuse type (undifferentiated type) gastric **carcinomas**. Our results thus suggest that **CDX2** and **CDX1** may play a role during IM formation and gastric **carcinogenesis**.

L3 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:731095 CAPLUS
DOCUMENT NUMBER: 135:285364
TITLE: Compositions and methods for identifying and targeting **cancer** cells
INVENTOR(S): Waldman, Scott A.; Park, Jason; Schulz, Stephanie
PATENT ASSIGNEE(S): Thomas Jefferson University, USA
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|------------|
| WO 2001073133 | A1 | 20011004 | WO 2001-US9918 | 20010327 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| US 2001029019 | A1 | 20011011 | US 2001-819249 | 20010327 |
| US 2001029020 | A1 | 20011011 | US 2001-819254 | 20010327 |
| US 2001036635 | A1 | 20011101 | US 2001-819247 | 20010327 |
| US 2001039016 | A1 | 20011108 | US 2001-819248 | 20010327 |
| US 2001039017 | A1 | 20011108 | US 2001-819252 | 20010327 |
| | | | US 2000-192229 | P 20000327 |

PRIORITY APPLN. INFO.:

AB **Screening** and **diagnostic** reagents, kits and methods for metastatic colorectal **cancer** or primary and/or

Searcher : Shears 308-4994

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metastatic stomach or esophageal **cancer** are disclosed.
Compds., compns. and methods of treating patients with metastatic
colorectal **cancer** or stomach or esophageal **cancer**
and for imaging metastatic colorectal **cancer** or stomach or
esophageal **tumors** in vivo are disclosed. Compns. and
methods for delivering active compds. such as drugs, gene
therapeutics and antisense compds. to metastatic colorectal
cancer or stomach or esophageal cells are disclosed.
Vaccines compns. and methods of for treating and preventing
metastatic colorectal **cancer** or primary and/or metastatic
stomach or esophageal **cancer** are disclosed.

L3 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:731093 CAPLUS
DOCUMENT NUMBER: 135:269675
TITLE: High specificity marker **detection**
INVENTOR(S): Waldman, Scott A.; Fava, Tracy; Desnoyers,
Rodwige
PATENT ASSIGNEE(S): Thomas Jefferson University, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|------------|
| WO 2001073131 | A1 | 20011004 | WO 2001-US9789 | 20010327 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| US 2001029019 | A1 | 20011011 | US 2001-819249 | 20010327 |
| US 2001029020 | A1 | 20011011 | US 2001-819254 | 20010327 |
| US 2001036635 | A1 | 20011101 | US 2001-819247 | 20010327 |
| US 2001039016 | A1 | 20011108 | US 2001-819248 | 20010327 |
| US 2001039017 | A1 | 20011108 | US 2001-819252 | 20010327 |
| | | | US 2000-192229 | P 20000327 |

PRIORITY APPLN. INFO.:

AB This invention provides methods of **detecting** the presence of a disseminated cell marker in a sample by eliminating illegitimate transcription-pos. cells from the sample and **detecting** the presence of mRNA that encodes the marker. CD34+ cells are removed by column chromatog. before **detecting** marker mRNA by PCR. This invention also provides methods of **detecting** disseminated **cancer** cells. Total RNA from mononuclear cells obtained from Dukes' stage D patients was serially dild. and analyzed by RT-PCR employing guanylyl cyclase C (GC-C)- and CEA-specific primers. GC-C and CEA transcripts **detected** employing <1 .mu.g of RNA reflect circulating **tumor** cells in blood. CEA amplicons were

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detected in 7/24 (~30 %) and 5/24 (~21 %) Dukes' stage D **cancer** patients employing 0.8 .mu.g or 0.5 .mu.g of RNA, resp. In contrast, all (n=24) stage D patients yielded GC-C transcripts employing .gtoreq.0.1 .mu.g of RNA.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:634833 CAPLUS
DOCUMENT NUMBER: 135:329860
TITLE: Expression of the gut-enriched Kruppel-like factor (Kruppel-like factor 4) gene in the human colon **cancer** cell line RKO is dependent on **CDX2**

AUTHOR(S): Dang, Duyen T.; Mahatan, Channing S.; Dang, Long H.; Agboola, Iyabode A.; Yang, Vincent W.
CORPORATE SOURCE: Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Oncogene (2001), 20(35), 4884-4890
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Gut-enriched Kruppel-like factor (GKLF or KLF4) is a zinc finger-contg., epithelial-specific transcription factor, that functions as a suppressor of cell proliferation. We previously showed that GKLF expression is decreased in intestinal and colonic adenomas, resp., from multiple intestinal **neoplasia** (Min) mice and familial adenomatous polyposis (FAP) patients. This study shows that GKLF is induced upon activation of the adenomatous polyposis coli (APC) gene. However, among several human colon **cancer** cell lines surveyed, expression of GKLF is lowest in RKO, a line with wild-type APC and .beta.-catenin. RKO contains a mutated allele that encodes the putative **tumor** suppressor homeodomain protein, **CDX2**. We show that wild-type **CDX2** activates the GKLF promoter and that the mutated **CDX2** has a dominant neg. effect on wild-type function. Our results may help explain the exceedingly low levels of GKLF expression **detected** in this cell line, which may in turn contribute to the **tumor** phenotype.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:507728 CAPLUS
DOCUMENT NUMBER: 135:121178
TITLE: Identification of colon **cancer** -associated proteins for immunotherapy and **diagnosis**

INVENTOR(S): Xu, Jiangchun; Lodes, Michael J.; Secrist, Heather; Benson, Darin R.; Meagher, Madeleine Joy; Stolk, John A.; King, Gordon E.; Wang, Tongtong; Jiang, Yuqiu
PATENT ASSIGNEE(S): Corixa Corporation, USA
SOURCE: PCT Int. Appl., 472 pp.

Searcher : Shears 308-4994

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DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|------------|
| WO 2001049716 | A2 | 20010712 | WO 2000-US35596 | 20001229 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| PRIORITY APPLN. INFO.: | | | US 1999-476296 | A 19991230 |
| | | | US 2000-480321 | A 20000110 |
| | | | US 2000-504629 | A 20000215 |
| | | | US 2000-519444 | A 20000306 |
| | | | US 2000-575251 | A 20000519 |
| | | | US 2000-609448 | A 20000629 |
| | | | US 2000-649811 | A 20000828 |

AB The authors disclose the use of a cDNA library and subtractive PCR to identify a no. of genes, and their proteins, which are overexpressed in human colon tumors. In addn., sol. tumor proteins expressed in serum of colon tumor-bearing SCID mice were used to generate polyclonal antibodies for probing a cDNA expression library.

L3 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:476371 CAPLUS
DOCUMENT NUMBER: 136:51964
TITLE: CDX2 mutations do not account for juvenile polyposis or Peutz-Jeghers syndrome and occur infrequently in sporadic colorectal cancers
AUTHOR(S): Woodford-Richens, K. L.; Halford, S.; Rowan, A.; Bevan, S.; Aaltonen, L. A.; Wasan, H.; Bicknell, D.; Bodmer, W. F.; Houlston, R. S.; Tomlinson, I. P. M.
CORPORATE SOURCE: Molecular and Population Genetics Laboratory, Imperial Cancer Research Fund, London, WC2A 3PX, UK
SOURCE: British Journal of Cancer (2001), 84(10), 1314-1316
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peutz-Jeghers syndrome (PJS) and juvenile polyposis (JPS) are both characterized by the presence of hamartomatous polyps and increased risk of malignancy in the gastrointestinal tract. Mutations of the LKB1 and SMAD4 genes have been shown recently to cause a no. of PJS

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and JPS cases resp., but there remains considerable uncharacterized genetic heterogeneity in these syndromes, particularly JPS. The mouse homolog of **CDX2** has been shown to give rise to a phenotype which includes hamartomatous-like polyps in the colon and is therefore a good candidate for JPS and PJS cases which are not accounted for by the SMAD4 and LKB1 genes. By analogy with SMAD4, **CDX2** is also a candidate for somatic mutation in sporadic colorectal cancer. We have screened 37 JPS families/cases without known SMAD4 mutations, 10 Peutz-Jeghers cases without known LKB1 mutations and 49 sporadic colorectal cancers for mutations in **CDX2**. Although polymorphic variants and rare variants of unlikely significance were detected, no pathogenic **CDX2** mutations were found in any case of JPS or PJS, or in any of the sporadic cancers

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:208293 CAPLUS

DOCUMENT NUMBER: 134:247973

TITLE: T-type calcium channel CACNA1G polynucleotide and polypeptide and methylation of CpG islands of CACNA1G and related genes associated with tumors

INVENTOR(S): Issa, Jean-Pierre
PATENT ASSIGNEE(S): The Johns Hopkins University School of Medicine, USA

SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|----------|
| WO 2001019845 | A1 | 20010322 | WO 2000-US25479 | 20000914 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |

PRIORITY APPLN. INFO.:

AB A novel T-type calcium channel (CACNA1G) is provided, as are polynucleotides encoding the same. CACNA1G has been implicated in cellular proliferative disorders. More specifically, it has been obsd. that the methylation state of specific regions within CpG islands assocd. with the CACNA1G gene correlates with a no. of cancerous phenotypes involving a variety of tissue and cell types. Also provided are methods for detecting cellular proliferative disorders by detg. the methylation state of

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genes or regulatory regions assocd. therewith, including CACNA1G, as well as kits contg. reagents for performing invention methods. Using a recently developed PCR-based technique called methylated CpG island amplification (MCA), several nucleic acid mols. aberrantly methylated in a colon **cancer** cell line were identified, on of which (termed MINT31) mapped to human chromosome 17q21 where frequent loss of heterozygosity has been **detected** in various human **tumors**. The invention provides methylated forms of the CpG islands of human genes APOB, CACNA1G, **CDX2**, EGFR, FRN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, and SDC4.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:155660 CAPLUS

DOCUMENT NUMBER: 135:135130

TITLE: Differential expression of Hox A5 in human colon **cancer** cell differentiation: a

AUTHOR(S): quantitative study using real-time RT-PCR
Wang, Yuxun; Hung, Carrie; Koh, Dawn; Cheong, Denis; Hooi, Shing Chuan

CORPORATE SOURCE: Department of Physiology, National University of Singapore, Singapore, 119260, Singapore

SOURCE: Int. J. Oncol. (2001), 18(3), 617-622

CODEN: IJONES; ISSN: 1019-6439

PUBLISHER: International Journal of Oncology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Fifteen different homeobox genes were identified from normal colon mucosa, untreated COLO 205 and herbimycin A treated COLO 205 cells in a degenerate primer RT-PCR **screen**. Several of the homeobox genes, including Cdx-1, **Cdx-2**, Pdx-1 and Hox A5, showed a trend toward differential expression in normal colon mucosa, and undifferentiated COLO 205 cells. Hox A5 was recently shown to suppress growth and induce p53-dependent apoptosis. To **det.** if Hox A5 was differentially expressed in differentiation of colon epithelial cells, the authors quantified Hox A5 expression by real-time quant. RT-PCR. Expression of Hox A5 was 5.3- and 4.8-fold higher in normal colon mucosa compared to COLO 205 and HT-29 cells, resp., suggesting that Hox A5 expression was higher in differentiated compared to undifferentiated colon epithelial cells. To avoid the complexity of tissue specimens and the influence of individual variation in Hox A5 expression, the effect of differentiation on Hox A5 expression was studied in COLO 205 cells treated with herbimycin A. The quant. study showed that Hox A5 expression was increased when COLO 205 cells were induced to differentiate. The expression of Hox A5 was about 2-fold higher in the cells treated for 48 h compared to the untreated poorly-differentiated cells. The present study shows that Hox A5 may be involved in intestinal cell differentiation, in addn. to its role in apoptosis.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2002 ACS

Searcher : Shears 308-4994

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ACCESSION NUMBER: 2001:121299 CAPLUS
DOCUMENT NUMBER: 135:90622
TITLE: The homeobox gene **CDX2** in colorectal
carcinoma: A genetic analysis
AUTHOR(S): Sivagnanasundaram, S.; Islam, I.; Talbot, I.;
Drummond, F.; Walters, J. R. F.; Edwards, Y. H.
CORPORATE SOURCE: MRC Human Biochemical Genetics Unit, Biology
Department, University College London, London,
NW1 2HE, UK
SOURCE: Br. J. Cancer (2001), 84(2), 218-225
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Accumulation of mutations in **tumor** suppressor genes and
oncogenes has been proposed to underlie the initiation and
progression of sporadic colorectal **cancer** (CRC). Evidence
is accumulating to suggest that the caudal homeobox gene
CDX2 is implicated in the pathogenesis of CRC. The
CDX2 transcription factor is expressed in intestinal
epithelium and is markedly down-regulated in colon **tumors**.
Furthermore, **Cdx2** heterozygous null mice develop multiple
intestinal **tumors**. In this present study, the authors
have investigated **CDX2** as a potential candidate gene for
sporadic CRC by a thorough search of all exons and exon/intron
boundaries for DNA polymorphisms and rare variants in a panel of CRC
tumors. Six polymorphisms were identified and the
haplotypes **detd.** In addn. two rare variants were found,
one of which was only identified in DNA from a CRC case. Loss of
heterozygosity was obsd. in 3 out of 28 informative CRC cases. A
possible assocn. between particular haplotypes and **tumor**
progression was also suggested by the data. In addn. a preliminary
anal. of the relative expression of **CDX2** alleles in
tumor/normal tissue suggested some variation in the levels;
however, further anal. is required before any conclusions can be
drawn. While **CDX2** mutations predisposing to sporadic CRC
have not been identified, this study has established that loss of
CDX2 contributes towards the progression of some sporadic
CRC **tumors**.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L3 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:824448 CAPLUS
DOCUMENT NUMBER: 134:1380
TITLE: **CDX2** is downstream mediator of APC
tumor suppressor activity
INVENTOR(S): Dacosta, Luis; Vogelstein, Bert; Kinzler,
Kenneth W.; He, Tong-chuan
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

Searcher : Shears 308-4994

09/819252

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|----------|
| WO 2000070089 | A1 | 20001123 | WO 2000-US12893 | 20000512 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |

PRIORITY APPLN. INFO.:

US 1999-311551 A1 19990514

AB Human **CDX2**, a homeobox gene, has been identified as a downstream effector of **tumor** suppressor APC (adenomatous polyposis coli protein). APC induces the transcription of **CDX2**. This newly found relationship permits specific drug **screening** assays as well as therapeutic and **diagnostic** methods. A test substance which increases expression in the cell of the **CDX2** gene product (mRNA or protein) is a candidate drug for treating human **cancers** with mutant APC alleles.

REFERENCE COUNT:


9

THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:601290 CAPLUS

DOCUMENT NUMBER: 133:279647

TITLE:  Distinct expression of **CDX2** and GATA4/5, development-related genes, in human gastric **cancer** cell lines

AUTHOR(S): Bai, Yun-Qing; Akiyama, Yoshimitsu; Nagasaki, Hiromi; Yagi, Osmar Kenji; Kikuchi, Yoko; Saito, Naoya; Takeshita, Kimiya; Iwai, Takehisa; Yuasa, Yasuhito

CORPORATE SOURCE: Department of Surgery, Tokyo Medical and Dental University School of Medicine, Tokyo, 113-8519, Japan

SOURCE: Mol. Carcinog. (2000), 28(3), 184-188
CODEN: MOCAE8; ISSN: 0899-1987

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **CDX2** is a **tumor**-suppressor homeobox gene involved in colon **carcinogenesis**, but its role in gastric **cancer** is unknown. Although GATA4, -5 and, -6 transcription factors have distinct functions in the regulation of gastrointestinal epithelial cell differentiation, there have been no reports regarding GATA4/5/6 alterations in gastrointestinal **carcinomas**. By using a semiquant. reverse transcription-polymerase chain reaction assay, we studied the expression of gut development-related genes **CDX2/1** and GATA4/5/6 in 11 human gastric **cancer** cell lines. The expression of **CDX2** appeared to progressively decrease with the transition from well differentiated to poorly differentiated **cancer** cell lines. **CDX1** was below **detectable** levels in all cell lines. The expression of GATA4 and GATA5 was

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undetectable in four and six cell lines, resp., whereas the majority of the cell lines expressed GATA6 abundantly. These results suggest that **CDX2** and GATA4/5 may be assocd. with the **carcinogenesis** of the stomach.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L3 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:575060 CAPLUS
DOCUMENT NUMBER: 134:276326
TITLE: Identification of novel polymorphisms in the
AXIN1 and **CDX-2** genes
AUTHOR(S): Lin, Yu-Min; Kato, Tatsushi; Satoh, Seiji;
Nakamura, Yusuke; Furukawa, Yoichi
CORPORATE SOURCE: Laboratory of Molecular Medicine, The University
of Tokyo, Tokyo, 108-8639, Japan
SOURCE: J. Hum. Genet. (2000), 45(4), 254-256
CODEN: JHGEFR; ISSN: 1434-5161
PUBLISHER: Springer-Verlag Tokyo
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Axin and **Cdx-2** play important roles in the
tumorigenesis of human liver and colon. We have identified seven
novel single-nucleotide polymorphisms (SNPs) in the AXIN1 gene and
three in the **CDX-2** gene. The identification of
SNPs in these **cancer**-assocd. genes establishes a basis for
future investigations to **detect** losses of heterozygosity
in **tumors**; these SNPs may also provide genetic background
information assocd. with **cancer** risk.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L3 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:408051 CAPLUS
DOCUMENT NUMBER: 131:180767
TITLE: Colonic hamartoma development by anomalous
duplication in **Cdx2** knockout mice
AUTHOR(S): Tamai, Yoshitaka; Nakajima, Reiko; Ishikawa,
Tomo-O.; Takaku, Kazuaki; Seldin, Michael F.;
Taketo, Makoto M.
CORPORATE SOURCE: Banyu Tsukuba Research Institute (Merck),
Ibaraki, 300-2611, Japan
SOURCE: Cancer Res. (1999), 59(12), 2965-2970
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To **det.** the biol. role of caudal-like homeobox gene
CDX2, the authors constructed knockout mice in which its
mouse homolog **Cdx2** was inactivated by homologous
recombination, placing a bacterial lacZ gene under the control of
the **Cdx2** promoter. Although the homozygous mutants died
in utero around implantation, the heterozygotes were viable and
fertile and expressed lacZ in the caudal region in early embryos and
in the gut tissues in adults. The heterozygotes developed cecal and
colonic villi by anteriorization and formed hamartomatous polyps in

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the proximal colon. The hamartoma started to develop at 11.5 days of gestation as an outpocket of the gut epithelium, which ceased to express the remaining **Cdx2** allele. The outpocket then expanded as a partially duplicated gut but was contained as a hamartoma after birth. In adult mice, these hamartomas grew very slowly and took a benign course. None of them progressed into invasive adenocarcinomas, even at 1.5 yr of age. Whereas the cecal and colonic villi expressed lacZ, the hamartoma epithelium did not, nor did it express **Cdx2** mRNA from the wild-type allele. However, genomic DNA anal. of the polyp epithelium did not show a loss of heterozygosity of the **Cdx2** gene, suggesting a mechanism of biallelic **Cdx2** inactivation other than loss of heterozygosity. These results indicate that the **Cdx2** haploinsufficiency caused cecal and colonic villi, whereas the biallelic inactivation of **Cdx2** triggered anomalous duplications of the embryonic gut epithelium, which were contained as hamartomas after birth.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L3 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:133041 CAPLUS

DOCUMENT NUMBER: 131:28476

TITLE: Genomic structure and alterations of homeobox
gene **CDX2** in colorectal
carcinomas

AUTHOR(S): Yagi, O. K.; Akiyama, Y.; Yuasa, Y.
CORPORATE SOURCE: First Department of Surgery, Tokyo Medical and
Dental University School of Medicine, Tokyo,
113-8519, Japan

SOURCE: Br. J. Cancer (1999), 79(3/4), 440-444
CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Expression of **CDX2**, a caudal-related homeobox gene, was
found to be decreased in colorectal **carcinomas**.
Heterozygous null mutant mice as to **Cdx2** develop multiple
intestinal adenomatous polyps. To clarify the role of **CDX2**
in colorectal **carcinogenesis**, we detd. its
genomic structure, and searched for mutations of **CDX2** in
49 sporadic colorectal **carcinomas** and ten hereditary
non-polyposis colorectal **cancers** (HNPCC) without
microsatellite instability. None of them exhibited a mutation. We
further examd. 19 HNPCC **carcinomas** with microsatellite
instability for mutations in a (G)7 repeat site within **CDX2**.
One of them (5.3%) exhibited one G insertion. Loss of
heterozygosity was obsd. in 2 of the 20 (10%) informative sporadic
carcinomas, and in one of the three (33.3%) informative
HNPCC **cancers**. These data indicate that **CDX2**
may play only a minor role in colorectal **carcinogenesis**.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L3 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:471951 CAPLUS

Searcher : Shears 308-4994

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DOCUMENT NUMBER: 129:243173
TITLE: Growth control mechanisms in normal and transformed intestinal cells
AUTHOR(S): Burgess, Antony W.
CORPORATE SOURCE: Ludwig Inst. Cancer Res., Melbourne, 3050, Australia
SOURCE: Philos. Trans. R. Soc. London, Ser. B (1998), 353(1370), 903-909
CODEN: PTRBAE; ISSN: 0962-8436
PUBLISHER: Royal Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 67 refs. The cells populating the intestinal crypts are part of a dynamic tissue system which involves the self-renewal of stem cells, a commitment to proliferation, lineage-specific differentiation, movement, and cell death. The knowledge of these processes is limited, but even now there are important clues to the nature of the regulatory systems, and these clues are leading to a better understanding of intestinal **cancers**. Few intestinal-specific markers have been described; however, homeobox genes such as **cdx-2** appear to be important for morphogenic events in the intestine. There are several intestinal cell surface proteins such as the A33 antigen which have been used as targets for immunotherapy. Many regulatory cytokines (lymphokines or growth factors) influence intestinal development: enteroglucagon, IL-2, FGF, EGF family members. In conjunction with cell-cell contact and/or ECM, these cytokines lead to specific differentiation signals. Although the tissue distribution of mitogens such as EGF, TGF.alpha., amphiregulin, betacellulin, HB-EGF and crypto have been studied in detail, the physiol. roles of these proteins have been difficult to **det.** Clearly, these mitogens and the corresponding receptors are involved in the maintenance and progression of the tumorigenic state. The interactions between mitogenic, **tumor** suppressor and oncogenic systems are complex, but the tumorigenic effects of multiple lesions in intestinal **carcinomas** involve synergistic actions from lesions in these difference systems. Together, the truncation of apc and activation of the ras oncogene are sufficient to induce colon tumorigenesis. If **cancer** therapy is to be improved, it is imperative that the biol. significance of these interactions, in particular the effects on cell division, movement, and survival, are discovered.

L3 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:165501 CAPLUS
DOCUMENT NUMBER: 128:240304
TITLE: Mammalian gene Cdx mutations as homologs of Drosophila gene caudal mutations for **diagnosing** and treating colon **cancer**
INVENTOR(S): Beck, Felix; James, Robert; Chawengsaksophak, Kallayanee
PATENT ASSIGNEE(S): Howard Florey Institute of Experimental Physiology and Medicine, Australia; Beck, Felix; James, Robert; Chawengsaksophak, Kallayanee
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

Searcher : Shears 308-4994

09/819252

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|----------|-----------------|----------|
| WO 9809510 | A1 | 19980312 | WO 1997-AU564 | 19970901 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| CA 2184780 | AA | 19980305 | CA 1996-2184780 | 19960904 |
| AU 9740035 | A1 | 19980326 | AU 1997-40035 | 19970901 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | AU 1996-2108 | 19960904 |
| | | | CA 1996-2184780 | 19960904 |
| | | | US 1996-25610 | 19960904 |
| | | | WO 1997-AU564 | 19970901 |

AB The present invention relates generally to methods of **diagnosing** and treating **cancer** and more particularly colon **cancer**. Even more particularly, the present invention provides a genetically manipulated live animal model (preferably mouse) comprising a heterozygous mutation in a murine gene **Cdx2** (Drosophila caudal gene homolog) useful for developing **diagnostic** and treatment protocols for colon **cancer**. The present invention further provides agents useful for **diagnosing** and treating colon **cancer** in animals such as mammals including humans. Antibodies to all or part of **Cdx2** for use in **screening** of **Cdx2** expression are also claimed.

L3 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:194390 CAPLUS

DOCUMENT NUMBER: 126:208069

TITLE: Molecular cloning, sequencing and expression of the mRNA encoding human **Cdx1** and **Cdx2** homeobox. Down-regulation of **Cdx1** and **Cdx2** mRNA expression during colorectal **carcinogenesis**

AUTHOR(S): Mallo, Gustavo V.; Rechreche, Hocine; Frigerio, Jean-Marc; Rocha, Dominique; Zweibaum, Alain; Lacasa, Michel; Jordan, Bertrand R.; Dusetti, Nelson J.; Dagorn, Jean-Charles; Iovanna, Juan L.

CORPORATE SOURCE: U.315 INSERM, Marseille, F-13009, Fr.
SOURCE: Int. J. Cancer (1997), 74(1), 35-44
CODEN: IJCNAW; ISSN: 0020-7136

PUBLISHER: Wiley-Liss

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Defining the mol. mechanisms involved in **cancer** formation and progression is still a major challenge in colorectal-**cancer** research. Our strategy was to characterize genes whose expression is altered during colorectal **carcinogenesis**

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. To this end, the phenotype of a colorectal tumor was previously established by partial sequencing of a large no. of its transcripts and the genes of interest were selected by differential screening on high-d. filters with mRNA of colorectal cancer and normal adjacent mucosa. Fifty-one clones were found over-expressed, and 23 were under-expressed in the colorectal-cancer tissues of the 5 analyzed patients. Among the latter, clones 6G2 and 32D6 were found of particular interest, since they had significant homol. with several homeodomain-contg. genes. The highest degree of similarity was with the murine Cdx1 for 6G2, and with the murine Cdx2 and hamster Cdx3 for 32D6. Using a RT-PCR approach, complete sequence of both types of homeobox-contg. cDNA was obtained. The amino-acid sequence of the human Cdx1 is 85% identical to the mouse protein, and human Cdx2 has 94% identity with the mouse Cdx2 and hamster Cdx3. Tissue-distribution anal. of Cdx1 and Cdx2 mRNA showed that both transcripts were specifically expressed in small intestine, in colon and rectum. Twelve tissue samples from colorectal adenocarcinomas and the corresponding normal mucosa were analyzed by Northern blot. Expression of the 2 types of mRNA was either reduced or absent in 10 of them. Several colon-cancer cell lines were also analyzed. Cdx2 mRNA was absent from LS174T cells and Cdx1 mRNA was absent in PF11, TC7 and SW480 cells; none was detected in HT29 cells. It was concluded that decrease in human Cdx1 and/or Cdx2 expression is assocd. with colorectal tumorigenesis.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 11:04:22 ON 28 JAN 2002)

61 S L3

25 DUP REM L4 (36 DUPLICATES REMOVED)

L5 ANSWER 1 OF 25

MEDLINE

ACCESSION NUMBER: 2002064750 IN-PROCESS

DOCUMENT NUMBER: 21650199 PubMed ID: 11790453

TITLE: Ectopic expression of homeodomain protein CDX2 in intestinal metaplasia and carcinomas of the stomach.

AUTHOR: Bai Yun Qing; Yamamoto Hiroshi; Akiyama Yoshimitsu; Tanaka Hiroyuki; Takizawa Touichirou; Koike Morio; Kenji Yagi Osmar; Saitoh Kiyoshi; Takeshita Kimiya; Iwai Takehisa; Yuasa Yasuhito

CORPORATE SOURCE: Department of Surgery, Graduate School of Medicine and Dentistry, Tokyo Medical and Dental University, Tokyo, Japan.

SOURCE: CANCER LETTERS, (2002 Feb 8) 176 (1) 47-55. Journal code: 7600053. ISSN: 0304-3835.

PUB. COUNTRY: Ireland Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals

ENTRY DATE: Entered STN: 20020125

Last Updated on STN: 20020125

AB The roles of CDX2 and CDX1 homeobox genes during gastric carcinogenesis remain poorly defined. We have studied the expression of CDX2/1 in gastric cancers and intestinal metaplasia (IM) of 69 gastric carcinoma patients by immunohistochemistry. CDX2/1 were shown to be

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ectopically overexpressed in IM in 41 (85%) of 48, and 47 (90%) of 52 cases, respectively. The expression of **CDX2**/1 was detected in 38 (55%) and 51 (74%) of the 69 gastric carcinomas, respectively. The histological type of the gastric carcinomas was independently associated with **CDX2** expression, but not with that of **CDX1**, with higher **CDX2** expression in intestinal type (differentiated type) than in diffuse type (undifferentiated type) gastric carcinomas. Our results thus suggest that **CDX2** and **CDX1** may play a role during IM formation and gastric carcinogenesis.

DUPLICATE 1

L5 ANSWER 2 OF 25 MEDLINE
ACCESSION NUMBER: 2001695035 IN-PROCESS
DOCUMENT NUMBER: 21607907 PubMed ID: 11743638
TITLE: The Caudal-related homeodomain protein **CDX1** activates proliferating cell nuclear antigen expression in hepatocellular and colorectal carcinoma cells.
AUTHOR: Oh Eun-Jin; Park Jae-Hong; Cho Mong; Lee Won-Jae; Choi Yung Hyun; Yoo Mi-Ae
CORPORATE SOURCE: Department of Molecular Biology, Pusan National University, Pusan 609-735, Korea.
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (2002 Jan) 20 (1) 23-9.
PUB. COUNTRY: Greece
JOURNAL; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20011217
Last Updated on STN: 20020123
AB **Cdx1** and **Cdx2** are known as Caudal-related homeodomain transcription factors important in the early differentiation and maintenance of intestinal epithelial cells. **Cdx1** and **Cdx2** are expressed in the small intestine and colon of fetus and adult. Most previous studies suggested that **Cdx2** inhibits proliferation. Several target genes of **Cdx2** have been identified. However, the effect of **Cdx1** on cell proliferation is currently controversial and its target genes except for **Hox-A7** remain unknown. In this study, we found several potential Caudal-related homeodomain binding sequences in the 5'-flanking region of human PCNA gene. Cotransfection experiments, using human PCNA reporter plasmid and **CDX1** and **CDX2** expression plasmids, showed that **CDX1** transactivates human PCNA gene promoter activity in hepatocellular cell line (HepG2) and colorectal carcinoma cell lines (Colo320HSR and HCT116), while **CDX2** does not. **CDX1**-induced PCNA expression was also detected in immunoblot and cytochemistry experiments. In BrdU incorporation experiments, **CDX1** enhanced the incorporated BrdU. Taken together, our results suggest that **CDX1** have a pro-proliferative effect on proliferation through transactivation of PCNA promoter activity.

L5 ANSWER 3 OF 25 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-611641 [70] WPIDS
CROSS REFERENCE: 2001-616538 [65]; 2002-010726 [65]; 2002-025392 [74]; 2002-033805 [74]

Searcher : Shears 308-4994

09/819252

DOC. NO. CPI: C2001-182828
TITLE: In vitro **screening** for specific
gastrointestinal **cancer** cells, useful for
diagnosis, by **detecting**
expression of the markers SI, CDX1 or **CDX2**
DERWENT CLASS: B02 B04 D16 K08
INVENTOR(S): PARK, J; SCHULZ, S; WALDMAN, S A
PATENT ASSIGNEE(S): (UYJE-N) UNIV JEFFERSON THOMAS
COUNTRY COUNT: 95
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | | | | | | | | | | | | | | | |
|---------------|------|----------|-----------|----|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| WO 2001073133 | A1 | 20011004 | (200170)* | EN | 119 | | | | | | | | | | | | | | | |
| RW: | AT | BE | CH | CY | DE | DK | EA | ES | FI | FR | GB | GH | GM | GR | IE | IT | KE | LS | LU | MC |
| MW | MZ | NL | OA | PT | SD | SE | SL | SZ | TR | TZ | UG | ZW | | | | | | | | |
| W: | AE | AG | AL | AM | AT | AU | AZ | BA | BB | BG | BR | BY | BZ | CA | CH | CN | CO | CR | CU | CZ |
| DE | DK | DM | DZ | EE | ES | FI | GB | GD | GE | GH | GM | HR | HU | ID | IL | IN | IS | JP | KE | |
| KG | KP | KR | KZ | LC | LK | LR | LS | LT | LU | LV | MA | MD | MG | MK | MN | MW | MX | MZ | NO | |
| NZ | PL | PT | RO | RU | SD | SE | SG | SI | SK | SL | TJ | TM | TR | TT | TZ | UA | UG | US | UZ | |
| VN | YU | ZA | ZW | | | | | | | | | | | | | | | | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|------|----------------|----------|
| WO 2001073133 | A1 | WO 2001-US9918 | 20010327 |

PRIORITY APPLN. INFO: US 2000-192229P 20000327

AN 2001-611641 [70] WPIDS

CR 2001-616538 [65]; 2002-010726 [65]; 2002-025392 [74]; 2002-033805 [74]

AB WO 200173133 A UPAB: 20020117

NOVELTY - In vitro **screening** of metastatic colorectal **cancer** cells or primary and/or metastatic stomach or esophageal **cancer** cells by testing cells in extra-intestinal tissues and/or body fluids for expression of SI (sucrase isomaltase), CDX1 or **CDX2** (transcription factors). Expression of these markers indicates possible presence of the specified **cancer** cells.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) a similar method in which gene transcripts or translation products are **detected**;

in vitro method for confirming that a suspect cell is a colorectal, stomach or esophageal **tumor** cells by **detecting** expression of at least one of SI, CDX1 or **CDX2**;

(b) method for **diagnosing** stomach (or esophageal) **cancer** by **detecting** an SI transcription or translation product in a sample of stomach (or esophageal) tissue;

(c) kit for **detecting** colorectal, stomach or esophageal **cancer**;

(d) method for treating metastatic colorectal, stomach or esophageal **tumor** by administering a complex comprising a SI ligand (I) and an active agent (II);

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(e) method for radio-imaging metastatic colorectal, stomach or esophageal **tumor** by administering a complex comprising (I) and a **detectable** agent; and

(f) method for identifying a molecular marker for **detecting tumor** cells that have metastasized from an origin tissue to a destination tissue or fluid.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - None given in the source material.

USE - The method is used to **diagnose** (or monitor) metastatic colorectal **cancer** or primary and/or metastatic stomach or esophageal **cancer** cells, also to confirm identification of such cells. These **cancers** can be:

- (i) treated by administration of an SI ligand (I) and (optionally conjugated) cytostatic agent; or
- (ii) radioimaged by administering a conjugate of (I) and **detectable** agent.

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L5 ANSWER 4 OF 25 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-616538 [71] WPIDS
CROSS REFERENCE: 2001-611641 [65]; 2002-010726 [65]; 2002-025392
[74]; 2002-033805 [74]
DOC. NO. CPI: C2001-184681
TITLE: **Detecting** presence of disseminated cell
marker in a sample for **diagnosing**
metastatic **cancer**, involves eliminating
illegitimate transcription-positive cells from
sample and **detecting** presence of mRNA
encoding marker.
DERWENT CLASS: B04 D16
INVENTOR(S): DESNOYERS, R; FAVA, T; WALDMAN, S A
PATENT ASSIGNEE(S): (UYJE-N) UNIV JEFFERSON THOMAS
COUNTRY COUNT: 95
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|-----------------------------------------------------------------|------|----------|-----------|----|----|
| WO 2001073131 | A1 | 20011004 | (200171)* | EN | 56 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC | | | | | |
| MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW | | | | | |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ | | | | | |
| DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE | | | | | |
| KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO | | | | | |
| NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ | | | | | |
| VN YU ZA ZW | | | | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|------|----------------|----------|
| WO 2001073131 | A1 | WO 2001-US9789 | 20010327 |

PRIORITY APPLN. INFO: US 2000-192229P 20000327
AN 2001-616538 [71] WPIDS
CR 2001-611641 [65]; 2002-010726 [65]; 2002-025392 [74]; 2002-033805
[74]
AB WO 200173131 A UPAB: 20020117

Searcher : Shears 308-4994

09/819252

NOVELTY - **Detecting** (M1) the presence of a disseminated cell marker in a sample, comprising eliminating illegitimate transcription-positive cells from the sample, and **detecting** the presence of mRNA that encodes the marker, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) **detecting** (M2) the presence of tissue-specific marker in a sample not associated with the expression of the tissue-specific marker, comprising eliminating CD34+ cells from the sample, and **detecting** the presence of mRNA encoding the tissue-specific marker;

(2) **detecting** (M3) the presence of a disseminated cell in a sample, comprising eliminating CD34+ cells from the sample, and **detecting** the presence of mRNA that encodes a marker associated with the disseminated cell; and

(3) a kit (I) for **detecting** the presence of disseminated cell marker in a sample, preferably for **cancer** cells identified as from the primary **cancer** in a sample that does not normally express the marker, comprising an affinity column, and primers for **detecting** the presence of mRNA encoding the marker.

USE - M1 is useful for **detecting** the presence of a disseminated cell marker in a sample, and for **diagnosing** metastatic **cancer** by **detecting** the presence of a disseminated cell marker for **cancer** cells identified as from the primary **cancer** in a sample that does not normally express the marker (claimed).

Dwg.0/9

L5 ANSWER 5 OF 25 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-244777 [25] WPIDS
DOC. NO. CPI: C2001-073448
TITLE: New nucleic acid molecule for use as a marker for
screening cancer, comprises the
coding region for a T-type calcium channel and
regulatory sequences associated with the channel.
DERWENT CLASS: B04 D16
INVENTOR(S): ISSA, J
PATENT ASSIGNEE(S): (UYJO) UNIV JOHNS HOPKINS SCHOOL MEDICINE
COUNTRY COUNT: 93
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|-----------------------------------------------------------------|------|----------|-----------|----|-----|
| WO 2001019845 | A1 | 20010322 | (200125)* | EN | 125 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC | | | | | |
| MW MZ NL OA PT SD SE SL SZ TZ UG ZW | | | | | |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE | | | | | |
| DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG | | | | | |
| KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ | | | | | |
| PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU | | | | | |
| ZA ZW | | | | | |
| AU 2000075869 | A | 20010417 | (200140) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|-----------|------|-------------|------|
| ----- | | | |

Searcher : Shears 308-4994

09/819252

WO 2001019845 A1
AU 2000075869 A

WO 2000-US25479 20000914
AU 2000-75869 20000914

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|-----------------|----------|--------------|
| ----- | | |
| AU 2000075869 A | Based on | WO 200119845 |

PRIORITY APPLN. INFO: US 1999-398522 19990915

AN 2001-244777 [25] WPIDS

AB WO 200119845 A UPAB: 20010508

NOVELTY - An isolated nucleic acid molecule (I) comprising the coding region for a T-type calcium channel (CACNA1G) and regulatory sequences associated with the channel, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a purified polypeptide (II) encoded by a polynucleotide comprising a sequence (S1) of 3993 nucleotides fully defined in the specification;

(2) **detecting** (D) a cellular proliferative disorder in a subject, by contacting a nucleic acid-containing specimen from the subject with an agent that provides a **determination** of the methylation state of at least one gene or associated regulatory region of the gene, and identifying aberrant methylation of regions of the gene or regulatory region, where aberrant methylation is identified as being different when compared to the same regions of the gene or associated regulatory region in a subject not having the cellular proliferative disease;

(3) a kit for the **detection** of a cellular proliferative disorder in a subject, comprising carrier means compartmentalized to receive a sample, and containers including a container containing a reagent which modifies unmethylated cytosine and a second container containing primers for amplification of a CpG-containing nucleic acid, where the primer hybridizes with a target polynucleotide sequence (S2) of length ranging from 18-26 nucleotides, fully defined in the specification;

(4) isolated oligonucleotide primer(s) for **detection** of a methylated CpG-containing nucleic acid, capable of hybridizing with S2; and

(5) an isolated nucleic acid molecule (III) having at least one methylated cytosine of a CpG dinucleotide in a CpG-rich region, and encoding a gene selected from APOB, CACNA1G, **CDX2**, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 and SDC4.

USE - A cellular proliferative disorder can be **detected**, such as low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, gastric **cancer**, colorectal **cancer**, colorectal adenoma, acute myelogenous leukemia, lung **cancer**, renal **cancer**, leukemia, breast **cancer**, prostate **cancer**, endometrial **cancer** and neuroblastoma, in a subject (claimed). (I) is useful as a marker for **screening cancer**, risk assessment, prognosis, minimal residue disease identification, staging and identification of therapeutic targets.

ADVANTAGE - Identification of novel CACNA1G genes methylated in **cancer**, aging or diseases associated with aging increases the likelihood of finding genes methylated in particular **cancers**, increases the sensitivity and specificity of

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methylation **detection**, allows methylation profiling using multiple genes, and allows identification of new targets for therapeutic interventions.
Dwg.0/5

L5 ANSWER 6 OF 25 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2002-033805 [04] WPIDS
CROSS REFERENCE: 2001-611641 [65]; 2001-616538 [65]; 2002-010726 [65]; 2002-025392 [74]
DOC. NO. NON-CPI: N2002-026026
DOC. NO. CPI: C2002-009385
TITLE: **Diagnosing** and monitoring metastasis of colorectal, stomach or esophageal **cancer** by **detecting** the expression of the **CDX2** onco-gene or protein.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): PARK, J; SCHULZ, S; WALDMAN, S A
PATENT ASSIGNEE(S): (PARK-I) PARK J; (SCHU-I) SCHULZ S; (WALD-I) WALDMAN S A
COUNTRY COUNT: 1
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---------------|------|----------|-----------|----|----|
| US 2001039017 | A1 | 20011108 | (200204)* | | 18 |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|----------------|-----------------|----------|
| US 2001039017 | A1 Provisional | US 2000-192229P | 20000327 |
| | | US 2001-819252 | 20010327 |

PRIORITY APPLN. INFO: US 2000-192229P 20000327; US 2001-819252 20010327

AN 2002-033805 [04] WPIDS
CR 2001-611641 [65]; 2001-616538 [65]; 2002-010726 [65]; 2002-025392 [74]
AB US2001039017 A UPAB: 20020117
NOVELTY - Methods and kits for **diagnosing** and monitoring metastasis of colorectal, stomach or esophageal **cancer** by **detecting** the expression of the **CDX2** onco-gene or protein by polymerase and immunoassay, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) an in vitro method (I) of **screening** an individual for metastatic colorectal **cancer** cells or primary and/or metastatic stomach or esophageal **cancer** cells, comprising examining a sample of extra-intestinal tissue and/or body fluids from an individual to **determine** whether **CDX2** is being expressed by cells in the sample (expression of the **CDX2** indicates a possibility of metastatic colorectal **cancer** cells or primary and/or metastatic stomach or esophageal **cancer** cells in the sample);

(2) an in vitro method (II) of confirming that a **tumor** cell removed from a patient suspected of having colorectal, stomach or esophageal **cancer** cells is a colorectal, stomach or

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esophageal **tumor** cell, comprising **determining** whether a **tumor** cell expresses **CDX2** wherein expression of **CDX2** indicates that the **tumor** cell is a stomach or esophageal **tumor** cell;

(3) a method (III) of **diagnosing** an individual who has stomach or esophageal **cancer**, comprising the steps of examining a sample of stomach or esophageal tissue to **detect** the presence of **CDX2** transcript or translation product (the presence of **CDX2** transcript or translation product in a stomach sample indicates stomach or esophageal **cancer**); and

(4) a kit (IV) for **diagnosing** an individual who has colorectal, stomach and/or esophageal **cancer** comprising either:

(a) a container comprising polymerase chain reaction primers that selectively amplify **CDX2** gene transcript or cDNA generated from it; and

(b) 1 or more of:

(i) a container comprising a positive PCR assay control sample;

(ii) a container comprising a negative PCR assay control

sample;

(iii) instructions for obtaining and/or processing a sample;

(iv) instructions for performing a PCR **diagnostic**

assay, and

(v) photographs or illustrations depicting a positive result and/or a negative result of a PCR **diagnostic** assay; or

(c) a container comprising antibodies that specifically bind to **CDX2** gene translation product; and one or more of:

(i) a container comprising a positive immunoassay control sample;

(ii) a container comprising a negative immunoassay control sample;

(iii) instructions for obtaining and/or processing a sample;

(iv) instructions for performing an immuno-**diagnostic**

assay, and

(v) photographs or illustrations depicting a positive result and/or a negative result of an immuno **diagnostic** assay.

USE - The methods and kits are used for **diagnosing** and monitoring metastasis of colorectal, stomach or esophageal **cancer** (claimed).
Dwg.0/0

L5 ANSWER 7 OF 25 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2002-025392 [03] WPIDS
CROSS REFERENCE: 2001-611641 [65]; 2001-616538 [65]; 2002-010726
[65]; 2002-033805 [74]
DOC. NO. NON-CPI: N2002-019661
DOC. NO. CPI: C2002-006991
TITLE: Method for **detecting cancer**
metastases from colon, stomach, liver, throat,
thyroid, skin, brain and lung **tumors**.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): PARK, J; SCHULZ, S; WALDMAN, S A
PATENT ASSIGNEE(S): (PARK-I) PARK J; (SCHU-I) SCHULZ S; (WALD-I)
WALDMAN S A
COUNTRY COUNT: 1
PATENT INFORMATION:

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| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---------------|------|----------|-----------|----|----|
| US 2001039016 | A1 | 20011108 | (200203)* | | 5. |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|------|-------------|--------------------------|
| US 2001039016 | A1 | Provisional | US 2000-192229P 20000327 |
| | | | US 2001-819248 20010327 |

PRIORITY APPLN. INFO: US 2000-192229P 20000327; US 2001-819248 20010327

AN 2002-025392 [03] WPIDS
CR 2001-611641 [65]; 2001-616538 [65]; 2002-010726 [65]; 2002-033805 [74]

AB US2001039016 A UPAB: 20020117
NOVELTY - Method (I) for identifying molecular markers useful for **detecting tumor** cells metastasized from an origin tissue to a destination tissue or fluid, is new.
DETAILED DESCRIPTION - A method (I) for identifying a molecular marker useful for **detecting tumor** cells metastasized from an origin tissue to a destination tissue or fluid, comprising:

(a) down-regulating, in a population of origin tissue cells, the activity of a transcription factor associated with terminally differentiated origin tissue;

(b) comparing an expression profile of the population of down-regulated origin cells with the expression profile a population of control origin cells;

(c) identifying candidate markers which are expressed in the population of control origin cells but not in the population of down-regulated origin cells; and

(d) comparing expression of candidate markers in control population of origin cells **cancerous** population of origin cells and population of destination cells wherein a candidate marker that is express in the population of control origin cells and the population of **cancerous** origin cells and not in the population of destination cells is useful as a molecular marker for the **detection of cancer** metastasized from the origin tissue to the destination tissue or fluid.

USE - The method is used for **detecting cancer** metastases from colon, stomach, liver, throat, thyroid, skin, brain and lung **tumors** (claimed).

ADVANTAGE - The early **diagnosis of cancer** allows more effective treatment to be implemented. The method involves identifying candidate marker molecules associated with terminal differentiation in the tissue in which a **tumor** arises, and identifying marker molecules that are continued to be expressed in the **tumors** from that tissue but not in the biopsy tissue.

Dwg.0/5

L5 ANSWER 8 OF 25 MEDLINE
ACCESSION NUMBER: 2001476056 MEDLINE
DOCUMENT NUMBER: 21412304 PubMed ID: 11521200
TITLE: Expression of the gut-enriched Kruppel-like factor

DUPLICATE 2

Searcher : Shears 308-4994

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(Kruppel-like factor 4) gene in the human colon
cancer cell line RKO is dependent on
CDX2.

AUTHOR: Dang D T; Mahatan C S; Dang L H; Agboola I A; Yang V
W

CORPORATE SOURCE: Department of Medicine, The Johns Hopkins University
School of Medicine, Baltimore, Maryland, MD 21205,
USA.

CONTRACT NUMBER: CA84197 (NCI)
DK10020 (NIDDK)
DK52230 (NIDDK)

SOURCE: ONCOGENE, (2001 Aug 9) 20 (35) 4884-90.
Journal code: ONC; 8711562. ISSN: 0950-9232.

PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200109

ENTRY DATE: Entered STN: 20010827
Last Updated on STN: 20010910
Entered Medline: 20010906

AB Gut-enriched Kruppel-like factor (GKLF or KLF4) is a zinc
finger-containing, epithelial-specific transcription factor, that
functions as a suppressor of cell proliferation. We previously
showed that GKLF expression is decreased in intestinal and colonic
adenomas, respectively, from multiple intestinal **neoplasia**
(Min) mice and familial adenomatous polyposis (FAP) patients. This
study shows that GKLF is induced upon activation of the adenomatous
polyposis coli (APC) gene. However, among several human colon
cancer cell lines surveyed, expression of GKLF is lowest in
RKO, a line with wild-type APC and beta-catenin. RKO contains a
mutated allele that encodes the putative **tumor** suppressor
homeodomain protein, **CDX2**. We show that wild-type
CDX2 activates the GKLF promoter and that the mutated
CDX2 has a dominant negative effect on wild-type function.
Our results may help explain the exceedingly low levels of GKLF
expression **detected** in this cell line, which may in turn
contribute to the **tumor** phenotype.

L5 ANSWER 9 OF 25 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 2001264152 MEDLINE

DOCUMENT NUMBER: 21255383 PubMed ID: 11355940

TITLE: **CDX2** mutations do not account for juvenile
polyposis or Peutz-Jeghers syndrome and occur
infrequently in sporadic colorectal **cancers**

AUTHOR: Woodford-Richens K L; Halford S; Rowan A; Bevan S;
Aaltonen L A; Wasan H; Bicknell D; Bodmer W F;
Houlston R S; Tomlinson I P

CORPORATE SOURCE: Molecular and Population Genetics Laboratory,
Imperial Cancer Research Fund, London, WC2A 3PX, UK.

SOURCE: BRITISH JOURNAL OF CANCER, (2001 May 18) 84 (10)
1314-6.
Journal code: AV4; 0370635. ISSN: 0007-0920.

PUB. COUNTRY: Scotland: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

Searcher : Shears 308-4994

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ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010702
Last Updated on STN: 20010702
Entered Medline: 20010628

AB Peutz-Jeghers syndrome (PJS) and juvenile polyposis (JPS) are both characterized by the presence of hamartomatous polyps and increased risk of malignancy in the gastrointestinal tract. Mutations of the LKB1 and SMAD4 genes have been shown recently to cause a number of PJS and JPS cases respectively, but there remains considerable uncharacterized genetic heterogeneity in these syndromes, particularly JPS. The mouse homologue of **CDX2** has been shown to give rise to a phenotype which includes hamartomatous-like polyps in the colon and is therefore a good candidate for JPS and PJS cases which are not accounted for by the SMAD4 and LKB1 genes. By analogy with SMAD4, **CDX2** is also a candidate for somatic mutation in sporadic colorectal **cancer**. We have **screened** 37 JPS families/cases without known SMAD4 mutations, 10 Peutz-Jeghers cases without known LKB1 mutations and 49 sporadic colorectal **cancers** for mutations in **CDX2**. Although polymorphic variants and rare variants of unlikely significance were **detected**, no pathogenic **CDX2** mutations were found in any case of JPS or PJS, or in any of the sporadic **cancers**. Copyright 2001 **Cancer** Research Campaign.

L5 ANSWER 10 OF 25 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2001301009 MEDLINE
DOCUMENT NUMBER: 21110983 PubMed ID: 11179495
TITLE: Differential expression of Hox A5 in human colon **cancer** cell differentiation: a quantitative study using real-time RT-PCR.
AUTHOR: Wang Y; Hung C; Koh D; Cheong D; Hooi S C
CORPORATE SOURCE: Department of Physiology, Faculty of Medicine, National University of Singapore, Singapore 119260.
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (2001 Mar) 18 (3) 617-22.
JOURNAL CODE: CX5; 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
JOURNAL; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB Fifteen different homeobox genes were identified from normal colon mucosa, untreated COLO 205 and herbimycin A treated COLO 205 cells in a degenerate primer RT-PCR **screen**. Several of the homeobox genes, including Cdx-1, **Cdx-2**, Pdx-1 and Hox A5, showed a trend toward differential expression in normal colon mucosa, and undifferentiated COLO 205 cells. Hox A5 was recently shown to suppress growth and induce p53-dependent apoptosis. To **determine** if Hox A5 was differentially expressed in differentiation of colon epithelial cells, we quantified Hox A5 expression by real-time quantitative RT-PCR. Expression of Hox A5 was 5.3- and 4.8-fold higher in normal colon mucosa compared to COLO 205 and HT-29 cells, respectively, suggesting that Hox A5 expression was higher in differentiated

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compared to undifferentiated colon epithelial cells. To avoid the complexity of tissue specimens and the influence of individual variation in Hox A5 expression, the effect of differentiation on Hox A5 expression was studied in COLO 205 cells treated with herbimycin A. The quantitative study showed that Hox A5 expression was increased when COLO 205 cells were induced to differentiate. The expression of Hox A5 was about 2-fold higher in the cells treated for 48 h compared to the untreated poorly-differentiated cells. The present study shows that Hox A5 may be involved in intestinal cell differentiation, in addition to its role in apoptosis.

L5 ANSWER 11 OF 25 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001141827 MEDLINE
DOCUMENT NUMBER: 21094877 PubMed ID: 11161380
TITLE: The homeobox gene **CDX2** in colorectal
carcinoma: a genetic analysis.
AUTHOR: Sivagnanasundaram S; Islam I; Talbot I; Drummond F;
Walters J R; Edwards Y H
CORPORATE SOURCE: MRC Human Biochemical Genetics Unit, Biology
Department, University College London, Wolfson House,
4 Stephenson Way, London, NW1 2HE.
SOURCE: BRITISH JOURNAL OF CANCER, (2001 Jan) 84 (2) 218-25.
Journal code: AV4; 0370635. ISSN: 0007-0920.
PUB. COUNTRY: Scotland: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308
AB Accumulation of mutations in **tumour** suppressor genes and
oncogenes has been proposed to underlie the initiation and
progression of sporadic colorectal **cancer** (CRC). Evidence
is accumulating to suggest that the caudal homeobox gene
CDX2 is implicated in the pathogenesis of CRC. The
CDX2 transcription factor is expressed in intestinal
epithelium and is markedly down-regulated in colon **tumours**
. Furthermore, **Cdx2** heterozygous null mice develop
multiple intestinal **tumours**. In this present study, we
have investigated **CDX2** as a potential candidate gene for
sporadic CRC by a thorough search of all exons and exon/intron
boundaries for DNA polymorphisms and rare variants in a panel of CRC
tumours. 6 polymorphisms were identified and the haplotypes
determined. In addition two rare variants were found, one of
which was only identified in DNA from a CRC case. Loss of
heterozygosity was observed in 3 out of 28 informative CRC cases. A
possible association between particular haplotypes and
tumour progression was also suggested by the data. In
addition a preliminary analysis of the relative expression of
CDX2 alleles in **tumour**/normal tissue suggested
some variation in the levels, however further analysis is required
before any conclusions can be drawn. While **CDX2** mutations
predisposing to sporadic CRC have not been identified, this study
has established that loss of **CDX2** contributes towards the
progression of some sporadic CRC **tumours**. Copyright 2001
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L5 ANSWER 12 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001333887 EMBASE

TITLE: CDX-1 and CDX-2 are expressed in human colonic mucosa and are down-regulated in patients with Hirschsprung's disease associated enterocolitis.

AUTHOR: Lui V.C.H.; Li L.; Mai Har Sham; Tam P.K.H.

CORPORATE SOURCE: P.K.H. Tam, Division of Paediatric Surgery, Department of Surgery, Univ. of Hong Kong Medical Centre, Pokfulam, Hong Kong SAR, Hong Kong. paultam@hkucc.hku.hk

SOURCE: Biochimica et Biophysica Acta - Molecular Basis of Disease, (28 Sep 2001) 1537/2 (89-100). Refs: 37

PUBLISHER IDENT.: ISSN: 0925-4439 CODEN: BBADEX S 0925-4439(01)00056-4

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 007 Pediatrics and Pediatric Surgery

029 Clinical Biochemistry

048 Gastroenterology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Caudal type homeobox gene-1 and -2 (CDX-1 and CDX-2), homologues of the Drosophila homeobox gene caudal, encode transcription factors in endoderm derived tissues of the intestine. CDX genes control proliferation and differentiation of intestinal mucosal cells and colon **cancer** cells. Hirschsprung's Disease (HD) or congenital intestinal aganglioneosis, a major developmental anomaly of intestine, which causes functional intestinal obstruction, is frequently associated with enterocolitis. Aetiology of HD-associated enterocolitis (HDEC) remains obscure. Reduction of gut mucosal enteroendocrine cells, and inefficient transfer of the secretory immunoglobulin A across the gut mucosal cell were shown to be associated with enterocolitis in HD patients suggesting that mucosa may directly involve in the pathophysiology of HDEC. This study aims to ascertain whether the CDX-1 and CDX-2 genes, that control the proliferation and differentiation of mucosal cells, play a role in HDEC. Using semi-quantitative reverse transcription-polymerase chain reaction (RT-PCR) and in situ hybridisation, we analysed the expression of CDX-1 and CDX-2 genes in colon specimens of normal controls, necrotising enterocolitis (NEC) infants, and HD patients with and without enterocolitis. We showed for the first time that CDX-1 and CDX-2 genes were expressed in the colonic mucosal epithelium in normal, NEC and in HD infants. However, the expressions of both genes were reduced in patients with HDEC. Our findings suggest that reduced expression of CDX-1 and CDX-2 genes in mucosa may be associated with the development of HDEC. .COPYRGHT. 2001 Elsevier Science B.V. All rights reserved.

L5 ANSWER 13 OF 25 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2001-016251 [02] WPIDS

DOC. NO. CPI:

TITLE:

C2001-004556
Screening substances as candidate drugs for treating human **cancers** with mutant adenomatous polyposis coli alleles, involves

Searcher : Shears 308-4994

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contacting a human cell with a test substance and
monitoring **CDX2**-mediated expression.
B04 D16
DERWENT CLASS: DACOSTA, L; HE, T; KINZLER, K W; VOGELSTEIN, B
INVENTOR(S): (UYJO) UNIV JOHNS HOPKINS
PATENT ASSIGNEE(S): 92
COUNTRY COUNT:
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|-----------------------------------------------------------------|------|----------|-----------|----|----|
| WO 2000070089 | A1 | 20001123 | (200102)* | EN | 27 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC | | | | | |
| MW NL OA PT SD SE SL SZ TZ UG ZW | | | | | |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK | | | | | |
| DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP | | | | | |
| KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT | | | | | |
| RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA | | | | | |
| ZW | | | | | |
| AU 2000051304 | A | 20001205 | (200113) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|------|-----------------|----------|
| WO 2000070089 | A1 | WO 2000-US12893 | 20000512 |
| AU 2000051304 | A | AU 2000-51304 | 20000512 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---------------|------------|--------------|
| AU 2000051304 | A Based on | WO 200070089 |

PRIORITY APPLN. INFO: US 1999-311551 19990514

AN 2001-016251 [02] WPIDS

AB WO 200070089 A UPAB: 20010110

NOVELTY - **Screening** substances as candidate drugs for treating **cancers** with mutant adenomatous polyposis coli (APC) alleles, comprising contacting a human cell with a test substance, measuring expression of a **CDX2** gene product, **CDX2**-responsive gene product or **CDX2**-responsive reporter construct, e.g. mRNA or protein, is new. An increase in expression indicates that the substance is a candidate drug. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) ameliorating the effects of APC mutants on human cells, by administering a human wild-type **CDX2** coding sequence to human cells comprising mutant APC alleles, so that expression of **CDX2** is upregulated;
- (2) reducing risk of, or preventing, **tumors** in patients with Familial Adenomatous Polyposis, by administering a human wild-type **CDX2** coding sequence to intestinal cells of the patient, so that expression of **CDX2** is upregulated in the intestinal cells; and
- (3) **detecting** APC mutations, by measuring expression of human **CDX2** gene product, **CDX2**-responsive gene product or **CDX2**-responsive reporter gene product, comprising mRNA or protein, in a test sample containing human cells,

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comparing the measured expression in the test sample to the expression in a normal human control sample, where a diminished expression of human **CDX2** gene product in the test sample relative to the control suggests the presence of mutant APC alleles in the test sample.

ACTIVITY - Cytostatic.

No biological data is given.

MECHANISM OF ACTION - Regulator of **CDX2** gene expression; mediator of tumor suppressing activity.

USE - The method is useful for screening candidate drugs which are useful for treating human cancers with mutant adenomatous polyposis coli alleles. Wild-type **CDX2** is useful for reducing the risk of, or preventing tumors in, patients with Familial Adenomatous Polyposis, and for reducing or preventing the incidence of formation of tumors (claimed).

Dwg.0/4

L5 ANSWER 14 OF 25 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 2000:791004 SCISEARCH
THE GENUINE ARTICLE: 363RF
TITLE: Cdx1 and Cdx2 expression during intestinal development
AUTHOR: Silberg D G (Reprint); Swain G P; Suh E R; Traber P G
CORPORATE SOURCE: UNIV PENN, DEPT MED, DIV GASTROENTEROL, 415 CURIE BLVD, 650 CRB, PHILADELPHIA, PA 19104 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: GASTROENTEROLOGY, (OCT 2000) Vol. 119, No. 4, pp. 961-971.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 46
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background & Aims: The intestine-specific transcription factors Cdx1 and Cdx2 are candidate genes for directing intestinal development, differentiation, and maintenance of the intestinal phenotype. This study focused on the complex patterns of expression of Cdx1 and Cdx2 during mouse gastrointestinal development. Methods: Embryonic and postnatal mouse tissues were analyzed by immunohistochemistry to determine protein expression of Cdx1 and Cdx2 in the developing intestinal tract. Results: Cdx2 protein expression was observed at 9.5 postcoitum (pc), whereas weak expression of Cdx1 protein was first seen at 12.5 pc in the distal developing intestine (hindgut). Expression of Cdx1 increased from 13.5 to 14.5 pc during the endoderm/epithelial transition with predominately distal expression. In contrast to Cdx1, there was intense expression of Cdx2 in all but the distal portions of the developing intestine. Cdx2 expression remained low in the distal colon throughout postnatal development. A gradient of expression formed in the crypt-villus axis, with Cdx1 primarily in the crypt and Cdx2 primarily in the villus. Conclusions: Direct comparison of the patterns of Cdx1 and Cdx2 protein expression during

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development as performed in this study provides new insights into their potential functional roles. The relative expression of Cdx1 to **Cdx2** protein may be important in the anterior to posterior patterning of the intestinal epithelium and in defining patterns of proliferation and differentiation along the crypt-villus axis.

L5 ANSWER 15 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:224763 BIOSIS
DOCUMENT NUMBER: PREV200000224763
TITLE: Alteration of HOX and **CDX2** homeobox genes expression in colorectal **cancers** and adjacent mucosae.
AUTHOR(S): Poupon, Marie France (1); Moll, M. E.; Arvelo, F.; Bras-Goncalves, R.; Flagiello, D.; Malfoy, B.; Sastre, X.; Girodet, J.; Dutrillaux, B.
CORPORATE SOURCE: (1) Fac Sci Univ, Caracas Venezuela
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 367.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 16 OF 25 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000418931 MEDLINE
DOCUMENT NUMBER: 20401155 PubMed ID: 10944858
TITLE: Identification of novel polymorphisms in the AXIN1++ and **CDX-2** genes.
AUTHOR: Lin Y M; Kato T; Satoh S; Nakamura Y; Furukawa Y
CORPORATE SOURCE: Laboratory of Molecular Medicine, University of Tokyo, Japan.
SOURCE: JOURNAL OF HUMAN GENETICS, (2000) 45 (4) 254-6.
Journal code: CYJ; 9808008. ISSN: 1434-5161.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000901

AB Axin and **Cdx-2** play important roles in the tumorigenesis of human liver and colon. We have identified seven novel single-nucleotide polymorphisms (SNPs) in the AXIN1 gene and three in the **CDX-2** gene. The identification of SNPs in these **cancer**-associated genes establishes a basis for future investigations to **detect** losses of heterozygosity in **tumors**; these SNPs may also provide genetic background information associated with **cancer** risk.

L5 ANSWER 17 OF 25 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000417264 MEDLINE
DOCUMENT NUMBER: 20400848 PubMed ID: 10942535

09/819252

TITLE: Distinct expression of **CDX2** and GATA4/5, development-related genes, in human gastric **cancer** cell lines.
AUTHOR: Bai Y; Akiyama Y; Nagasaki H; Yagi O K; Kikuchi Y; Saito N; Takeshita K; Iwai T; Yuasa Y
CORPORATE SOURCE: Department of Surgery, Tokyo Medical and Dental University School of Medicine, Tokyo, Japan.
SOURCE: MOLECULAR CARCINOGENESIS, (2000 Jul) 28 (3) 184-8. Journal code: AEQ; 8811105. ISSN: 0899-1987.
PUB. COUNTRY: United States
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000905

AB **CDX2** is a tumor-suppressor homeobox gene involved in colon **carcinogenesis**, but its role in gastric **cancer** is unknown. Although GATA4, -5 and, -6 transcription factors have distinct functions in the regulation of gastrointestinal epithelial cell differentiation, there have been no reports regarding GATA4/5/6 alterations in gastrointestinal **carcinomas**. By using a semiquantitative reverse transcription-polymerase chain reaction assay, we studied the expression of gut development-related genes **CDX2/1** and GATA4/5/6 in 11 human gastric **cancer** cell lines. The expression of **CDX2** appeared to progressively decrease with the transition from well differentiated to poorly differentiated **cancer** cell lines. **CDX1** was below **detectable** levels in all cell lines. The expression of GATA4 and GATA5 was **undetectable** in four and six cell lines, respectively, whereas the majority of the cell lines expressed GATA6 abundantly. These results suggest that **CDX2** and GATA4/5 may be associated with the **carcinogenesis** of the stomach. *Mol. Carcinog.* 28:184-188, 2000.

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L5 ANSWER 18 OF 25 CANCERLIT
ACCESSION NUMBER: 1999702172 CANCERLIT
DOCUMENT NUMBER: 99702172
TITLE: Abnormalities of Chromosome Bands 13q12-14 in Childhood Acute Lymphoblastic Leukemia (ALL) (Meeting abstract).
AUTHOR: Heerema Nyla; Sensel Martha; Sather Harland; Nachman James; Hutchinson Raymon; Reaman Gregory; Lange Beverly; Steinherz Peter; Bostrom Bruce; Gaynon Paul; Arthur Diane; Uckun Fatih
CORPORATE SOURCE: CCG ALL Biology Reference Laboratory, Hughes Institute, St. Paul, MN.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, (1999). Vol. 18, pp. A2181.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199910
AB Nonrandom deletions of 13q are frequent in B-cell chronic lymphocytic leukemia, but very little is known about this

Searcher : Shears 308-4994

abnormality in B-lineage acute leukemias. In the current report, we describe 36 cases of newly **diagnosed** pediatric ALL with breakpoints in 13q12-14. All patients were treated on recent protocols (1989-1995) of the Children's **Cancer** Group. The majority of these patients had favorable presenting features including white race, female sex, age 1-9 years, B-lineage immunophenotype, WBC counts <20,000/L, and moderate or no organomegaly. Overall, eight cases had balanced rearrangements of 13q12-14 and 28 patients had partial loss of 13q, including 20 with partial deletions of 13q; three with loss of 13q12 or q14 to 13qter; and five with loss of 13pter to 13q12. In five patients, the abnormal 13q was the sole aberration. Seven patients also had an abnormal 12p, two with a t (12;13) (p13;q12). Four patients had a del (6q), four had a del (9p), three had breakpoints in 14q11, and two had an 11q23 breakpoint. Nineteen patients were pseudodiploid; ten were hyperdiploid (one with >50 chromosomes and nine with 47-50 chromosomes); seven were hypodiploid. Of the 36 patients, 26 are survivors: 21 have survived event-free 3.3 to 8.7 years and five patients remain alive 1.4 months to 5 years after a relapse. Recently, t (12;13) (p13;q12) in acute myeloid leukemia was shown to result in production of the fusion gene TEL-CDX2 and t (8;13) (p11;q12) in myeloproliferative syndromes was shown to result in production of the fusion gene ZNF198-FGFR1, both of which are likely to have altered regulatory properties that may contribute to tumorigenesis. These findings raise the possibility that aberrations of 13q12-14 may also contribute to leukemogenesis of childhood ALL. (C) American Society of Clinical Oncology 1999.

L5 ANSWER 19 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 8

ACCESSION NUMBER: 1999:321196 BIOSIS
DOCUMENT NUMBER: PREV199900321196
TITLE: Colonic hamartoma development by anomalous duplication in **Cdx2** knockout mice.
AUTHOR(S): Tamai, Yoshitaka; Nakajima, Reiko; Ishikawa, Tomo-o; Takaku, Kazuaki; Seldin, Michael F.; Taketo, Makoto M. (1)
CORPORATE SOURCE: (1) Laboratory of Biomedical Genetics, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo, 113-0033 Japan
SOURCE: Cancer Research, (June 15, 1999) Vol. 59, No. 12, pp. 2965-2970.
ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB To **determine** the biological role of caudal-like homeobox gene **CDX2**, we constructed knockout mice in which its mouse homologue **Cdx2** was inactivated by homologous recombination, placing a bacterial lacZ gene under the control of the **Cdx2** promoter. Although the homozygous mutants died in utero around implantation, the heterozygotes were viable and fertile and expressed lacZ in the caudal region in early embryos and in the gut tissues in adults. The heterozygotes developed cecal and colonic villi by anteriorization and formed hamartomatous polyps in the proximal colon. The hamartoma started to develop at 11.5 days of gestation as an out-pocket of the gut epithelium, which ceased to express the remaining **Cdx2** allele. The outpocket then

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expanded as a partially duplicated gut but was contained as a hamartoma after birth. In adult mice, these hamartomas grew very slowly and took a benign course. None of them progressed into invasive adenocarcinomas, even at 1.5 years of age. Whereas the cecal and colonic villi expressed lacZ, the hamartoma epithelium did not, nor did it express **Cdx2** mRNA from the wild-type allele. However, genomic DNA analysis of the polyp epithelium did not show a loss of heterozygosity of the **Cdx2** gene, suggesting a mechanism of biallelic **Cdx2** inactivation other than loss of heterozygosity. These results indicate that the **Cdx2** haploin-sufficiency caused cecal and colonic villi, whereas the biallelic inactivation of **Cdx2** triggered anomalous duplications of the embryonic gut epithelium, which were contained as hamartomas after birth.

L5 ANSWER 20 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1999:108555 BIOSIS

DOCUMENT NUMBER: PREV199900108555

TITLE: Fusion of ETV6 to the caudal-related homeobox gene **CDX2** in acute myeloid leukemia with the t(12;13)(p13;q12).

AUTHOR(S): Chase, Andrew; Reiter, Andreas; Burci, Linda; Cazzaniga, Giovanni; Biondi, Andrea; Pickard, Julie; Roberts, Irene A. G.; Goldman, John M.; Cross, Nicholas C. P.

CORPORATE SOURCE: Dep. Haematol., Imperial Coll. Sch. Med., Hammersmith Hosp., Du Cane Rd., London W12 0NN UK

SOURCE: Blood, (Feb. 1, 1999) Vol. 93, No. 3, pp. 1025-1031. ISSN: 0006-4971.

DOCUMENT TYPE: Article

LANGUAGE: English

AB The t(12;13)(p13;q12) is a rare, recurrent translocation reported in a range of hematological malignancies. We have analyzed the molecular basis of this lesion in three patients with acute myeloid leukemia (AML), two of whom were known to have chromosome 12 breakpoints within the ETV6 gene. Fluorescence in situ hybridization (FISH) with ETV6 cosmid indicated that this gene was also disrupted in the third patient, while the normal ETV6 allele was retained. 3' rapid amplification of cDNA ends (RACE) polymerase chain reaction (PCR) from bone marrow mRNA of this individual identified a novel sequence fused to ETV6 that was homologous to a region just upstream of the mouse **CDX2** homeobox gene, the human homologue of which has previously been mapped to chromosome 13q12. PCR primers designed to amplify an ETV6-**CDX2** fusion identified two major transcripts from this patient. First, a direct in-frame fusion between exon 2 of ETV6 and exon 2 of **CDX2**, and second, a transcript that had an additional sequence of unknown origin spliced between these same exons. Surprisingly, apparently normal **CDX2** transcripts, usually expressed only in intestinal epithelium, were also detectable in cDNA from this patient. Neither normal nor fusion **CDX2** mRNA was detectable in the two other patients with a t(12;13), indicating that this translocation is heterogeneous at the molecular level. Reverse transcription-PCR analysis showed that **CDX2** mRNA, but not ETV6-**CDX2** mRNA, was strongly expressed in 1 of 10 patients with chronic myeloid leukemia in transformation, suggesting that deregulation of this gene may be more widespread in leukemia. **CDX2** is known to regulate class I homeobox genes

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and its expression in hematopoietic cells may critically affect the balance between differentiation and proliferation.

DUPLICATE 9

L5 ANSWER 21 OF 25 MEDLINE
ACCESSION NUMBER: 1999149556 MEDLINE
DOCUMENT NUMBER: 99149556 PubMed ID: 10027310
TITLE: Genomic structure and alterations of homeobox gene
CDX2 in colorectal **carcinomas**.
AUTHOR: Yagi O K; Akiyama Y; Yuasa Y
CORPORATE SOURCE: First Department of Surgery, Tokyo Medical and Dental
University School of Medicine, Japan.
SOURCE: BRITISH JOURNAL OF CANCER, (1999 Feb) 79 (3-4) 440-4.
Journal code: AV4; 0370635. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990324
Last Updated on STN: 19990324
Entered Medline: 19990305

AB Expression of **CDX2**, a caudal-related homeobox gene, was found to be decreased in colorectal **carcinomas**. Heterozygous null mutant mice as to **Cdx2** develop multiple intestinal adenomatous polyps. To clarify the role of **CDX2** in colorectal **carcinogenesis**, we determined its genomic structure, and searched for mutations of **CDX2** in 49 sporadic colorectal **carcinomas** and ten hereditary non-polyposis colorectal **cancers** (HNPCC) without microsatellite instability. None of them exhibited a mutation. We further examined 19 HNPCC **carcinomas** with microsatellite instability for mutations in a (G)7 repeat site within **CDX2**. One of them (5.3%) exhibited one G insertion. Loss of heterozygosity was observed in 2 of the 20 (10%) informative sporadic **carcinomas**, and in one of the three (33.3%) informative HNPCC **cancers**. These data indicate that **CDX2** may play only a minor role in colorectal **carcinogenesis**.

L5 ANSWER 22 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999239371 EMBASE
TITLE: Expression and regulation of the meprin .beta. gene in human **cancer** cells.
AUTHOR: Matters G.L.; Bond J.S.
CORPORATE SOURCE: J.S. Bond, Dept. of Biochem./Molec. Biol. H171, Pennsylvania State Univ. Coll. Med., Hershey, PA 17033-0850, United States
SOURCE: Molecular Carcinogenesis, (1999) 25/3 (169-178).
Refs: 36
ISSN: 0899-1987 CODEN: MOCAE8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A novel mRNA isoform (meprin .beta.) of the cell-surface protease subunit meprin .beta. was previously identified in human colon **cancer** cells. The study reported here revealed that this

Searcher : Shears 308-4994

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mRNA isoform was identical within the protein coding region and at the 3' end to the .beta. isoform of normal intestine but that it contained an extended 5' untranslated region. Meprin .beta.' mRNA was expressed in the human breast **cancer** cell lines MCF-7 and SK-BR-3, in the human osteosarcoma cell line U2 Os, and in the human pancreatic **cancer** cell line BxPC-3. Meprin .beta. mRNA, but not .beta.' mRNA, was expressed in human fetal kidney cells. We cloned and sequenced genomic DNA encoding portions of the promoter region of the meprin .beta. gene. The unique sequences present in the .beta.' mRNA were present in the human genomic DNA immediately upstream of the transcription start site for the .beta. mRNA. The human meprin promoter sequence was searched for potential transcription-factor binding sites, and putative activator protein-1, polyoma enhancer activator 3 (PEA3), CCAAT enhancer-binding protein beta, and estrogen-receptor binding sites were identified along with binding sites for the intestine-specific **cdx-2** transcription factor. The activity of meprin promoter/luciferase reporter gene constructs transfected into U2 Os cells was highest with constructs containing 83 and 639 bp of promoter DNA. These regions of the promoter each contain a putative PEA3 element. Treatment of the human colon adenocarcinoma cell line HT29- 18C1 with 50 or 100 ng/mL phorbol myristal acetate for 8 h increased meprin .beta.' mRNA levels. Likewise, U2 Os cells transfected with the -639/luciferase or -1800/luciferase constructs showed a phorbol myristal acetate-inducible increase in reporter gene activity, indicating that the PEA3 element within the -639 construct or other elements further upstream respond to phorbol ester.

L5 ANSWER 23 OF 25 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1998-193247 [17] WPIDS
DOC. NO. NON-CPI: N1998-152966
DOC. NO. CPI: C1998-061826
TITLE: Animal model having a **Cdx2** Drosophila
caudal gene homologue mutation - useful for
developing **diagnostic** and treatment
protocols for colon **cancer**.
DERWENT CLASS: B04 D16 P14 S03
INVENTOR(S): BECK, F; CHAWENGSAKSOPHAK, K; JAMES, R
PATENT ASSIGNEE(S): (FLOR-N) FLOREY INST EXPERIMENTAL PHYSIOLOGY
COUNTRY COUNT: 78
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|-----------------------------------------------------------------|------|----------|-----------|----|----|
| WO 9809510 | A1 | 19980312 | (199817)* | EN | 51 |
| RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL | | | | | |
| OA PT SD SE SZ UG ZW | | | | | |
| W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI | | | | | |
| GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD | | | | | |
| MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR | | | | | |
| TT UA UG US UZ VN YU ZW | | | | | |
| AU 9740035 | A | 19980326 | (199832) | | |
| CA 2184780 | A | 19980305 | (199832) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|-----------|------|-------------|------|
|-----------|------|-------------|------|

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| | | | |
|------------|----|-----------------|----------|
| WO 9809510 | A1 | WO 1997-AU564 | 19970901 |
| AU 9740035 | A | AU 1997-40035 | 19970901 |
| CA 2184780 | A | CA 1996-2184780 | 19960904 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|------------|------|------------|
| AU 9740035 | A | WO 9809510 |

PRIORITY APPLN. INFO: US 1996-25610P 19960904; AU 1996-2108
19960904; CA 1996-2184780 19960904

AN 1998-193247 [17] WPIDS
AB WO 9809510 A UPAB: 19980428
A genetically altered animal, or progeny of the animal, having a predisposition to develop growth of **neoplastic** cells in intestinal epithelium, is claimed.
Also claimed are: (1) an antibody to all or part of **Cdx2** for use in **screening** for the presence or absence of **Cdx2** expression; (1) an isolated nucleic acid molecule comprising a nucleotide sequence encoding a human homologue of *Drosophila* caudal gene **Cdx2**; and (3) an isolated human **Cdx2** protein including a recombinant form with at least 60 % similarity to a 311 amino acid residue sequence (given in the specification).

USE - The genetically altered animal is useful as a model for **carcinoma** of the colon or a precursor stage of colon **cancer**. **Cdx2** antibodies are useful for **detecting Cdx2** in biological samples. The presence of a mutation in at least one **Cdx2** allele is indicative of a predisposition to developing familial **carcinoma** of the colon or **diagnosis** of colon **cancer** (All claimed). Modulators of **Cdx2** are useful for modulating the expression of **Cdx2** in humans. Non-mutated **Cdx2** genes can be used to reduce the likelihood of development of colon **cancer** or reduce the spread of colon **cancer** in a subject. (All claimed).
Dwg.0/4

L5 ANSWER 24 OF 25 MEDLINE
ACCESSION NUMBER: 1998348912 MEDLINE
DOCUMENT NUMBER: 98348912 PubMed ID: 9684287
TITLE: Growth control mechanisms in normal and transformed intestinal cells.
AUTHOR: Burgess A W
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Melbourne, Australia.. burgess@ludwig.edu.au
SOURCE: PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY OF LONDON. SERIES B: BIOLOGICAL SCIENCES, (1998 Jun 29) 353 (1370) 903-9. Ref: 67
Journal code: P5Z; 7503623. ISSN: 0962-8436.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals

DUPLICATE 10

Searcher : Shears 308-4994

09/819252

ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980903
Last Updated on STN: 20000303
Entered Medline: 19980821

AB The cells populating the intestinal crypts are part of a dynamic tissue system which involves the self-renewal of stem cells, a commitment to proliferation, lineage-specific differentiation, movement and cell death. Our knowledge of these processes is limited, but even now there are important clues to the nature of the regulatory systems, and these clues are leading to a better understanding of intestinal **cancers**. Few intestinal-specific markers have been described; however, homeobox genes such as **cdx-2** appear to be important for morphogenic events in the intestine. There are several intestinal cell surface proteins such as the A33 antigen which have been used as targets for immunotherapy. Many regulatory cytokines (lymphokines or growth factors) influence intestinal development: enteroglucagon, IL-2, FGF, EGF family members. In conjunction with cell-cell contact and/or ECM, these cytokines lead to specific differentiation signals. Although the tissue distribution of mitogens such as EGF, TGF alpha, amphiregulin, betacellulin, HB-EGF and cripto have been studied in detail, the physiological roles of these proteins have been difficult to **determine**. Clearly, these mitogens and the corresponding receptors are involved in the maintenance and progression of the tumorigenic state. The interactions between mitogenic, **tumour** suppressor and oncogenic systems are complex, but the tumorigenic effects of multiple lesions in intestinal **carcinomas** involve synergistic actions from lesions in these different systems. Together, the truncation of **apc** and activation of the **ras** oncogene are sufficient to induce colon tumorigenesis. If we are to improve **cancer** therapy, it is imperative that we discover the biological significance of these interactions, in particular the effects on cell division, movement and survival.

L5 ANSWER 25 OF 25 MEDLINE
ACCESSION NUMBER: 97188282 MEDLINE
DOCUMENT NUMBER: 97188282 PubMed ID: 9036867
TITLE: Molecular cloning, sequencing and expression of the mRNA encoding human Cdx1 and **Cdx2** homeobox. Down-regulation of Cdx1 and **Cdx2** mRNA expression during colorectal **carcinogenesis**
AUTHOR: Mallo G V; Rechreche H; Frigerio J M; Rocha D; Zweibaum A; Lacasa M; Jordan B R; Dusetti N J; Dagorn J C; Iovanna J L
CORPORATE SOURCE: U.315 INSERM, Marseille, France.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1997 Feb 20) 74 (1) 35-44.
PUB. COUNTRY: Journal code: GQU; 0042124. ISSN: 0020-7136.
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-T24426; GENBANK-T24427; GENBANK-T24428; GENBANK-T24429; GENBANK-T24430; GENBANK-T24431; GENBANK-T24432; GENBANK-T24433; GENBANK-T24434; GENBANK-T24435; GENBANK-T24436; GENBANK-T24437;

DUPLICATE 11

Searcher : Shears 308-4994

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GENBANK-T24438; GENBANK-T24439; GENBANK-T24440;
GENBANK-T24441; GENBANK-T24442; GENBANK-T24443;
GENBANK-T24444; GENBANK-T24445; GENBANK-T24446;
GENBANK-T24447; GENBANK-T24448; GENBANK-T24449;
GENBANK-T24450; GENBANK-T24451; GENBANK-T24452;
GENBANK-T24453; GENBANK-T24454; GENBANK-T24455; +
199703

ENTRY MONTH:

ENTRY DATE:

Entered STN: 19970327

Last Updated on STN: 19980206

Entered Medline: 19970320

AB Defining the molecular mechanisms involved in **cancer** formation and progression is still a major challenge in colorectal-**cancer** research. Our strategy was to characterize genes whose expression is altered during colorectal **carcinogenesis**. To this end, the phenotype of a colorectal **tumour** was previously established by partial sequencing of a large number of its transcripts and the genes of interest were selected by differential **screening** on high-density filters with mRNA of colorectal **cancer** and normal adjacent mucosa. Fifty-one clones were found over-expressed and 23 were underexpressed in the colorectal-**cancer** tissues of the 5 analyzed patients. Among the latter, clones 6G2 and 32D6 were found of particular interest, since they had significant homology with several homeodomain-containing genes. The highest degree of similarity was with the murine Cdx1 for 6G2, and with the murine **Cdx2** and hamster Cdx3 for 32D6. Using a RT-PCR approach, complete sequence of both types of homeobox-containing cDNA was obtained. The amino-acid sequence of the human Cdx1 is 85% identical to the mouse protein, and human **Cdx2** has 94% identity with the mouse **Cdx2** and hamster Cdx3. Tissue-distribution analysis of Cdx1 and **Cdx2** mRNA showed that both transcripts were specifically expressed in small intestine, in colon and rectum. Twelve tissue samples from colorectal adenocarcinomas and the corresponding normal mucosa were analyzed by Northern blot. Expression of the 2 types of mRNA was either reduced or absent in 10 of them. Several colon-**cancer** cell lines were also analyzed. **Cdx2** mRNA was absent from LS174T cells and Cdx1 mRNA was absent in PF11, TC7 and SW480 cells; none was **detected** in HT29 cells. It was concluded that decrease in human Cdx1 and/or **Cdx2** expression is associated with colorectal tumorigenesis.

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